UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,350	03/12/2004	Valery Krasnoperov	VASG-P01-002	2293

28120 7590 08/16/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/800,350	KRASNOPEROV ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-34 and 63-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-34 and 63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 6/16/06 in response to the Office Action of 2/14/06 are acknowledged and have been entered.

Claims 1-62 were pending.

Claims 1-25 and 57-58 were cancelled by Applicant.

Claims 63-68 have been added by Applicant.

Claims 35-56 and 59-62 were withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 26-33 have been amended by Applicant.

Claims 26-34 and 63-68 are currently under examination.

The text of those sections of Title 35 U.S.C. code not included in this Office Action can be found in a prior Office Action.

The following Office Action contains NEW GROUNDS of rejections necessitated by amendments.

Objections Withdrawn

The objections to the specification are withdrawn in view of amendments.

The objections to claims 26-34 are withdrawn in view of amendments.

Rejections Withdrawn

35 USC § 101

The rejections of claims 26-34 under 35 U.S.C. 101, for not distinguishing the claimed antibodies over antibodies as they exist naturally, are withdrawn in view of amendments.

35 USC § 102(b)

The rejections of claims 26-34 under 35 U.S.C. 102(b), as being anticipated by Stephenson et al (BMC Molecular Biology, 12/21/01, 2(15): 1-9) or Inada et al (Blood, 1997, 89(8): 2757-2765) as evidenced by Santa Cruz Biotechnology Inc datasheet for EphB4 (H-200), are withdrawn in view of amendments.

Rejections Maintained

Claims 26-34 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting, and newly added claims 63-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-23 of copending Application No. 10/949,720. Although the conflicting claims are not identical, they are not patentably distinct from each other because the antibodies of claims 1-23 of 10/949,720 anticipate the claimed cells and the genus of antibodies which bind to the extracellular domain of an EphB4 protein and inhibit activities of Ephb4 recited in the pending claims.

In the response filed 6/16/06, Applicant requests that the Examiner hold this rejection in abeyance until allowable subject matter is found: at which point, Applicants will submit a terminal disclaimer if deemed necessary.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 101

Claims 63 and 64 are rejected under 35 U.S.C. 101 because the claimed inventions are directed to non-statutory subject matter. Claim 63 does not distinguish over cells as they naturally exist in human beings that express human antibodies to the extracellular domain of EphB4 protein. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). Claim 63 should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105. Claims 63 and 64 are rejected since they read on transgenic human beings. Human beings are non-statutory subject matter (see MPEP 2105 [R-1]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-29, 31-34, and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stephenson et al (BMC Molecular Biology, 12/21/01, 2(15): 1-9) in view of Queen et al (US Patent 5,693,762; 12/2/97).

Claim 26 is drawn to an isolated antibody which binds to an extracellular domain of an EphB4 protein and promotes apoptosis in a tumor cell, wherein the antibody is selected from bispecific, single-chain, chimeric, human, syngeneic, and humanized antibodies. Claim 27 is drawn to the antibody of claim 26, wherein the antibody inhibits the interaction between Ephrin B2 and EphB4. Claim 28 is drawn to the antibody of claim 26 wherein the antibody inhibits clustering of EphB4. Claim 29 is drawn to the antibody of claim 26, wherein the antibody inhibits phosphorylation of EphB4. Claim 31 is drawn to the antibody of claim 26, wherein the antibody is a polyclonal antibody. Claim 32 is drawn to a pharmaceutical composition comprising the antibody of claim 26, and a pharmaceutically acceptable carrier. Claim 33 is drawn to a cosmetic composition comprising the antibody of claim 26 and a pharmaceutically acceptable

carrier. Claim 34 is drawn to a diagnostic kit comprising the antagonist antibody of claim 26 and a carrier. Claim 63 is drawn to a cell expressing the antibody of claim 26. Claim 64 is drawn to a transgenic animal expressing the antibody of claim 26. Claim 65 is drawn to the antibody of claim 26 further comprising a label attached thereto. Claim 66 is drawn to the antibody of claim 65 wherein the label is selected from a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Claim 67 is drawn to the antibody of claim 26, wherein the antibody inhibits angiogenesis. Claim 68 is drawn to the antibody of claim 26 wherein the antibody promotes tumor regression.

Stephenson et al teaches a polyclonal antibody and antibody kit available from Santa Cruz Biotechnology Inc (page 8 left column), EphB4 (H-200). As evidenced by Santa Cruz Biotechnology Inc datasheet for EphB4 (H-200), EphB4 (H-200) was raised against amino acids 201-400 mapping within the extracellular domain of human EphB4. Further, the datasheet states that the antibody is provided in a kit comprising a composition comprising the pharmaceutically acceptable carrier PBS. Further, Stephenson et al teaches that EphB4 protein is expressed on colon cancer tissues and either not at all, or in only low levels, in normal tissue (see Figure 4, in particular). Stephenson further teaches that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular). Due to the expression pattern of EphB2 protein, one of skill in the art would recognize that antibodies against EphB2 protein would also be used in methods of diagnosing colon cancer.

Queen et al (US Patent 5,693,762; 12/2/97) teaches novel methods for producing, and compositions of, humanized immunoglobulins (see column 2-3 and 12-

16, in particular). Queen et al also teaches antibody fragments and bifunctional antibodies (i.e. bispecific antibodies) (see column 11, lines 6-9 and 18-25, in particular). Queen et al also teach chimeric antibodies (column 1 lines 56-59, in particular). Queen et al also teaches single chain antibodies (column 17 lines 42-44, in particular). Queen et al further teaches antibodies conjugated to a variety of cytotoxic agents including radioisotopes, chemotherapeutic drugs, toxins for therapeutic purposes and antibodies labeled with fluorescent compounds, enzymes or enzyme co-factors for diagnostic purposes (see column 20, lines 1-35). Queen et al further teaches that CDRs for producing antibodies can be obtained from mice, rats, rabbits, or other vertebrates capable of producing antibodies (see paragraph spanning columns 16 and 17, in particular). Queen et al further teaches that the antibodies are created by expressing antibody constructs in cells and animals (see column 18 lines 29-31 and column 40 lines 62-64, in particular). Queen et al further teaches antibodies diluted in a pharmaceutically acceptable carrier for administration of said antibodies (see column 23, lines 55-61, in particular). Queen et al further teaches that, as compared to non-recombinant mouse monoclonal antibodies and non-recombinant rabbit polyclonal antibodies, humanized antibodies are expected to (i) interact better with the human immune system (i.e. CDC and ADCC), (ii) reduce the HAMA response and (iii) the humanized antibodies will "presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and les fragment doses to be given" (see column 16, lines 6-26). Further, one of skill in the art would recognize that bispecific (bifunctional) antibodies have the obvious therapeutic advantage of recruiting effector

molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to a protein target on a cancer cell. Further, Queen et al teaches that chimeric antibodies have proven to be therapeutically successful in some instances (column 1 lines 56-59, in particular). Further, one of skill in the art would recognize that single chain antibodies have an obvious therapeutic advantage, due to their smaller size, of penetrating deeper into tumors than the immunoglobulins from which they derive.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Stephenson et al with the teachings of Queen et al to create kits comprising radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific, single chain, chimeric, and humanized polyclonal antibodies specific for the extracellular domain of EphB4 in pharmaceutically acceptable carriers. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Stephenson et al with the teachings of Queen et al to create kits comprising radioisotope, fluorescent, enzyme, and enzyme co-factor labeled isolated human antibodies specific for the extracellular domain of EphB4 in pharmaceutically acceptable carriers. Further, one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific antibodies because bispecific antibodies would function as diagnostic and therapeutic agents that recruit effector molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to the

colon cancer cells expressing EphB4. Further, one have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled single chain antibodies because said antibodies would be more successful at targeting diagnostics and therapeutics to EphB4 expressing colon cancer cells than the entire immunoglobulin molecule taught by Stephenson et al. Further, one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled chimeric antibodies since chimeric antibodies have shown some therapeutic success. Further, one would have been motivated to isolate said human antibodies and to create radioisotope, fluorescent, enzyme, and enzyme co-factor labeled humanized antibodies because, as compared to non-recombinant mouse monoclonal antibodies and non-recombinant rabbit polyclonal antibodies, human and humanized antibodies would be more effective diagnostically and therapeutically effective because they are expected to (i) interact better with the human immune system (i.e. CDC and ADCC), (ii) reduce the HAMA response and (iii) the humanized antibodies will presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and les fragment doses to be given. Further, cells and transgenic animals expressing single chain, chimeric, and humanized antibodies specific for the extracellular domain of EphB4 would be created while creating the antibodies taught by the combined teachings of Stephenson et al and Queen et al. Further, one of skill in the art would have a reasonable expectation of success in producing and/or isolating the claimed antibodies and antibody constructs since methods of creating radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific, single chain, chimeric, and

humanized antibodies, and methods of isolating human antibodies are well known and conventional in the art. Further, one of skill in the art would have a reasonable expectation of success in producing cells and transgenic animals expressing single chain, chimeric, and humanized antibodies specific for the extracellular domain of EphB4 because methods of creating cells and transgenic animals expressing single chain, chimeric, and humanized antibodies are well known and conventional in the art.

Further, one of skill in the art would recognize that the antibodies taught by the combined teachings of Stephenson et al and Queen et al would inhibit activities of EphB4. Absent a showing otherwise, the antibodies taught by the combined teachings of Stephenson et al and Queen et al would inhibit the interaction between Ephrin B2 and EphB4, inhibit clustering of EphB4, inhibit angiogenesis, and promote tumor regression. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the antibodies of the prior art do not possess the same characteristics as the claimed antibodies. In the absence of evidence to the contrary, the burden is on Applicant to prove that the claimed antibodies are different from those taught by the prior art and to establish patentable differences. See In re Best 562F .2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2nd 1992 (PTO Bd. Pat. App. & Int. 1989).

Claims 26-34, and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Inada et al (Blood, 1997, 89(8): 2757-2765), in view of Stephenson et

al (BMC Molecular Biology, 12/21/01, 2(15): 1-9) and in further view of Queen et al (US Patent 5,693,762; 12/2/97).

Claims 26-34, and 64-68 are described above. Claim 30 is drawn to the antibody of claim 26 wherein the antibody is a monoclonal antibody.

Inada et al teaches monoclonal (see Figure 2, page 2760) and polyclonal antibodies which bind to an extracellular domain of an EphB4 protein (page 2758, in particular), which this early reference refers to as HTK. One of skill in the art would recognize that purification of the antibodies would have involved producing a composition comprising the antibodies and a pharmaceutically acceptable carrier.

Stephenson et al teaches as described above.

Queen et al teaches as described above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Inada et al and Queen et al to use the monoclonal and polyclonal antibodies as taught by Inada et al with the methods taught by Queen et al to create kits comprising radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific, single chain, chimeric, and humanized monoclonal and polyclonal antibodies specific for the extracellular domain of EphB4 protein in pharmaceutically acceptable carriers. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Inada et al with the teachings of Queen et al to create kits comprising radioisotope, fluorescent, enzyme, and enzyme co-factor labeled isolated human antibodies specific for the extracellular domain of EphB4 in

pharmaceutically acceptable carriers. Further, one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific antibodies because Stephenson et al teaches EphB4 protein is a marker for colon cancer cells and bispecific antibodies would function as diagnostic and therapeutic agents that recruit effector molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to the colon cancer cells expressing EphB4. Further, one have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled single chain antibodies because Stephenson et al teaches EphB4 protein is a marker for colon cancer cells and said antibodies would be more successful at targeting diagnostics and therapeutics to EphB4 expressing colon cancer cells than the entire immunoglobulin molecules taught by Inada et al. Further, one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled chimeric antibodies because Stephenson et al teaches EphB4 protein is a marker for colon cancer cells and chimeric antibodies have shown some therapeutic success. Further, one would have been motivated to isolate said human antibodies and to create radioisotope, fluorescent, enzyme, and enzyme co-factor labeled humanized antibodies because Stephenson et al teaches EphB4 protein is a marker for colon cancer cells and, as compared to non-recombinant mouse monoclonal antibodies and non-recombinant rabbit polyclonal antibodies, human and humanized antibodies would be more effective diagnostic and therapeutic compounds because they are expected to (i) interact better with the human immune system (i.e. CDC and ADCC), (ii) reduce the

HAMA response and (iii) the humanized antibodies will presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and les fragment doses to be given. Further, cells and transgenic animals expressing single chain, chimeric, and humanized antibodies specific for EphB4 would be created while creating the antibodies taught by the combined teachings of Inada et al and Queen et al. Further, one of skill in the art would have a reasonable expectation of success in producing and/or isolating the claimed antibodies and antibody constructs since methods of creating radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific, single chain, chimeric, and humanized antibodies, and methods of isolating human antibodies are well known and conventional in the art. Further, one of skill in the art would have a reasonable expectation of success in producing cells and transgenic animals expressing single chain, chimeric, and humanized antibodies specific for the extracellular domain of EphB4 because methods of creating cells and transgenic animals expressing single chain, chimeric, and humanized antibodies are well known and conventional in the art.

Further, one of skill in the art would recognize that the antibodies taught by the combined teachings of Inada et al and Queen et al would inhibit activities of EphB4. Absent a showing otherwise, the antibodies taught by the combined teachings of Inada et al and Queen et al would inhibit the interaction between Ephrin B2 and EphB4, inhibit clustering of EphB4, inhibit angiogenesis, and promote tumor regression. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the antibodies of the prior art do not possess the same

characteristics as the claimed antibodies. In the absence of evidence to the contrary, the burden is on Applicant to prove that the claimed antibodies are different from those taught by the prior art and to establish patentable differences. See In re Best 562F .2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2nd 1992 (PTO Bd. Pat. App. & Int. 1989).

New Matter

Claims 26 and dependent claims 27-34 and 63-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claim 26 recites claims drawn to "human" and "syngeneic" antibodies that specifically bind the extracellular domain of an EphB4 protein. Descriptions of "human" and "syngeneic" antibodies that specifically bind the extracellular domain of an EphB4 protein are not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

Summary

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

SEA